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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,324	LARSEN ET AL.	
	Examiner	Art Unit	
	ROBERT T. CROW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87-140* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *87-140* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/17/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 15 September 2009 has been entered.

Status of the Claims

2. This action is in response to papers filed 15 September 2009 in which claims 89, 91-96, 99-100, 107-110, 117-120, 122-125, 127-129, 134-135 and 140 were amended, no claims were canceled, and no new claims were added. All of the amendments have been thoroughly reviewed and entered.

The Information Disclosure Statement filed 17 September 2009 is acknowledged and has been considered

The previous rejections under 35 U.S.C. 103(a) not reiterated below are withdrawn. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections.

Claims 87-140 are under prosecution.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 139 and 139 contain the trademark/trade names Cy3, Cy5, ad Cy5.5. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe chemical structures and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 108 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 108 is indefinite in the recitation "said targeting species" in line 2 of the claim. The recitation of "said targeting species" lacks antecedent basis in the "more than one first targeting species." It is suggested that the claim be amended to reflect proper antecedent basis.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 87-92, 95-102, 107-118, 120-130, and 137-140 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,451, issued 27 June 1995) in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) in view of Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) and, as applied to claim 91 as evidenced by Smith et al (J. Exp. Med., vol. 178, pages 2035-2046 (1 December 1993)).

Regarding claim 87, Lea et al teach a method for assessing at least one quality or quantity parameter of a particle in a liquid material utilizing a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45). Page 9 of the instant specification recites blood cells as a preferred form of particle. Thus, the blood cells of Lea et al are particles that have bound thereto or comprised therein less that $1x10^6$ analyte detectable positions per particle, and the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding "analytes in an amount of less than $1x10^6$ analyte detectable positions per particle " (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]). The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit

electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). Lea et al also teach a linear dimension of the image on the array to the original linear dimension image is smaller than 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). Because the entire image is magnified less than 20:1, each linear dimension of the image is magnified less than 20:1. The representation is detected as intensities by individual active detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images and the background is maximized (column 3, lines 50-67), and at least one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

While Lea et al teach particles that have bound thereto or comprised therein less that $1x10^6$ analyte detectable positions as described above, Lea et al do not explicitly teach the detected analytes are in an amount that is less than $1x10^6$.

However, Kaplan teaches a method wherein an analyte of interest in one or more cells or particles is detected (column 1, lines 64-67). The method uses magnetic particles that are bound to the cells in order to retain the cells (column 12, lines 25-40) to detect analytes that are present at less than 20,000 molecules/cell (or particle), which has the added advantage of detecting analytes that do not have to be overexpressed in a cell (i.e., the analytes are at their normal level in the cell; column 2, lines 15-25). Thus, Kaplan teaches the known technique of detecting analytes that are in an amount that is less than $1x10^6$ per particle.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method as taught by Lea et al so that the detected analytes are in an amount that is less than $1x10^6$ per particle as taught by Kaplan to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of allowing detection of analytes at their normal level in the cell (because the detected analytes do not have to be overexpressed in a cell) as explicitly taught by Kaplan (column 2, lies 15-25). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting analytes that are in an amount that is less than $1x10^6$ per particle as taught by Kaplan could have been applied to the method of Lea with predictable results because the known technique of detecting analytes that are in an amount that is less than $1x10^6$ per particle as taught by Kaplan predictably results in detection of analytes within a cell.

Lea et al teach that the particle stream speed should be controlled if the stream is moving too fast for accurate counting (column 3, lines 20-30). In addition, Kaplan et al teach the detection of analytes in a cell in the form of a plate (column 11, lines 30-55). While the cells/particles would not be flowing when placed in a plate, neither Lea et al nor Kaplan specifically teach the stream is at a standstill during the exposure of the signals onto the array of detectors.

However, Hansen et al teach a method wherein biological particles in a volume of liquid analyte material are assessed (paragraph 0001), wherein the particles and sample are detected at a standstill during the exposure (paragraph 0070), which has the added advantage of allowing the detection of any weak signals which might indicate the presence of a particle (paragraph 0051). Thus, Hansen et al teach the known technique of having a fluid stream at a standstill during the exposure of the signals onto the array of detectors.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method of Lea et al wherein particle stream speed should be controlled if the stream is moving too fast for accurate counting as suggested by Lea et al in view of Kaplan so that particle stream speed is controlled to a standstill during the exposure of the signals onto the array of detectors as taught by Hansen et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of improved sensitivity as a result of allowing the detection of any

weak signals which might indicate the presence of a particle as explicitly taught by Hansen et al (paragraph 0051). In addition, it would have been obvious to the ordinary artisan that the known technique of controlling the particle stream speed to a standstill during the exposure of the signals onto the array of detectors as taught by Hansen et al could have been applied to the method having controlled particle stream speed as taught by Lea et al in view of Kaplan with predictable results because the known technique of controlling the particle stream speed to a standstill during the exposure of the signals onto the array of detectors as taught by Hansen et al predictably results in improved sensitivity of detection.

Regarding claim 88, the method of claim 87 is discussed above. Lea et al teach the particle is a cell; namely, a blood cell (column 4, lines 25-45).

Regarding claim 89, the method of claim 88 is discussed above. Kaplan teaches the analyte is in or on the surface of a particle (column 4, lines 35-60). The particle is a non-cellular solid particle (column 3, lines 30-35), which is interpreted as a solid phase particle, which is taught by Kaplan to include beads (column 8, lines 15-25). Thus, modification of the method of Lea et al with the teachings of Kaplan and Hansen et al results in a method using beads as particles.

In addition, with respect to the claimed beads, the courts have found that changes in shape are obvious (*In re Dailey*, 357 F.2d 669, 149 USPQ 47 (CCPA 1966)). Thus, the claimed "beads" are obvious variants of the cell sized particles of Kaplan (column 3, lines 30-35). See MPEP 2144.04 [R-6] IV B.

Regarding claim 90, the method of claim 87 is discussed above. Kaplan also teaches the analyte is a protein (column 4, lines 35-55). Thus modification of the method of Lea et al with the teachings of Kaplan and Hansen et al results in analytes that are proteins.

Regarding claim 91, the method of claim 88 is discussed above. Kaplan further teaches the protein is MHC class I (column 4, lines 35-60), which is a membrane bound protein, as evidenced by Smith et al (page 2035). Thus modification of the method of Lea et al with the teachings of Kaplan and Hansen et al results in analytes that are membrane bound proteins.

Regarding claim 92, the method of claim 88 is discussed above. Kaplan further teaches the analyte is comprised in a cell; namely, the analyte is a molecule in a cell (column 4, lines 35-60). Thus modification of the method of Lea et al with the teachings of Kaplan and Hansen et al results in analytes that are in cells.

Regarding claims 95-96, the method of claim 87 is discussed above. Kaplan teaches the analyte is present at less than 20,000 molecules/cell (or particle; column 2, lines 15-25). Thus, modification of the method of Lea et al with the teachings of Kaplan and Hansen et al results in a method wherein the analyte is present in an amount between 500 and 50,000 molecules (i.e., claim 96), which is less than $5x10^5$ analyte detectable positions (i.e., claim 95).

Regarding claims 97-98, the method of claim 87 is discussed above. Lea et al teach also the cells are blood cells (i.e., claim 98; column 4, lines 25-45); blood cells encompass mammalian cells (i.e., claim 97). In addition, Kaplan teaches the cells are

blood cells (i.e., claim 98; column 8, lines 50-67) and mammalian cells (i.e., claim 97; column 3, lines 10-30). Thus, modification of the method of Lea et al with the teachings of Kaplan and Hansen et al results in a method wherein the particles are mammalian cells (i.e., claim 97), or blood cells (i.e., claim 98).

Regarding claim 99, the method of claim 87 is discussed above. Lea et al further teach the liquid material comprises at least two different species of particles; namely, the sample comprises biological cells and cells other than those of interest (column 4, line 25-column 5, line 5). The cells are particles and the cells other than those of interest are at least one additional species of particles in addition to the biological cells, which are a first species of particles.

Regarding claim 100, the method of claim 99 is discussed above. Lea et al teach only one of the species of particles has bound thereto or comprised therein the species of analyte; namely, the particles of interest are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). Because antibodies are highly specific, the antibodies bind only to one type of cell (i.e., particle) in the sample; namely, only to the cells having the analyte to which the antibodies bind.

Regarding claim 101, the method of claim 87 is discussed above. Kaplan teaches binding at least two distinct targeting species to at least two distinct species of analyte and labeling the at least two distinct targeting species with two distinct labeling agents; namely, a more than one analyte is detected by using a first binding partner

specific for a first analyte of interest, a second binding partner with enzymatic activity and which specifically binds to the first binding partner, a substrate for the enzymatic activity of the second binding partner, and a labeling molecule containing tyramide, followed by contacting with a third binding partner specific for a second analyte of interest, a fourth binding partner with enzymatic activity and which specifically binds to the third binding partner, a substrate for the enzymatic activity of the fourth binding partner, and a labeling molecule containing tyramide and specific for the fourth binding partners (column 6, lines 30-55). Thus, modification of the method of Lea et al with the teachings of Kaplan and Hansen et al results in a method comprising binding at least two distinct targeting species to at least two distinct species of analyte and labeling the at least two distinct targeting species with two distinct labeling agents.

Regarding claims 102 and 130, the method of claim 87 is discussed above. Kaplan also teaches the analyte is a Cluster of Differentiation marker (i.e., claim 102); namely, CD45 (column 4, lines 35-60 and Example 2).

Regarding claim 107, the method of claim 87 is discussed above. Lea et al also teach the at least one species of analyte is a medical marker of disease; namely, the counted cells are used to diagnose diseases (column 4, lines 25-40).

Regarding claim 108, the method of claim 87 is discussed above. Kaplan teaches the reagent material comprises more than one first targeting species, each of said targeting species being directed to a different analyte; namely, a more than one analyte is detected by using a first binding partner specific for a first analyte of interest and a third binding partner specific for a second analyte of interest (column 6, lines 30-

55). Thus, modification of the method of Lea et al with the teachings of Kaplan and Hansen et al results in a method comprising reagent material comprising more than one first targeting species, each of said targeting species being directed to a different analyte.

Regarding claim 109, the method of claim 87 is discussed above. Lea et al further teach the targeting species is an antibody to the analyte species; namely, the targeting species is the monoclonal antibody on the magnetic bead (column 4, line 25-column 5, line 5).

Regarding claim 110, the method of claim 87 is discussed above. Kaplan teaches the targeting species is a nucleotide probe complementary to a sequence of an analyte species; namely, the analyte is a nucleic acid, which binds to a binding partner that is also a nucleic acid (column 3, line 65-column 4, lines 60). Thus, modification of the method of Lea et al with the teachings of Kaplan and Hansen et al results in a method comprising a targeting species that is a nucleotide probe complementary to a sequence of an analyte species.

Regarding claim 111, the method of claim 87 is discussed above. Kaplan teaches the targeting species is an in situ hybridization probe; namely, the analyte is a nucleic acid, which binds to a binding partner that is also a nucleic acid (column 3, line 65-column 4, lines 60), and the probe is used for in situ hybridization (column 12, line 54-column 13, line 10). Thus, modification of the method of Lea et al with the teachings of Kaplan and Hansen et al results in a method comprising a targeting species that is an in situ hybridization probe.

Regarding claims 112 and 137, the method of claim 87 is discussed above. Lea et al teach the liquid material is a bodily fluid; namely, a blood sample (column 4, lines 25-40).

Regarding claim 113, the method of claim 87 is discussed above. Lea et al also teach the reagent material is an antibody labeled with a reactive moiety; namely, the reagent material is the bead having the antibody thereon, which is then reagent with an optical label in the form of a fluorescent dye (column 4, line 25-column 4, line 5). Because the dye reacts with the antibody/bead, the antibody is labeled with a reactive moiety; i.e., the group that reacts with the dye.

Regarding claim 114, the method of claim 87 is discussed above. Kaplan teaches the reagent material is a fluorescently labeled nucleotide probe; namely, the analyte is a nucleic acid, which binds to a fist binding partner that is also a nucleic acid (column 3, line 65-column 4, lines 60), and the first binding partner is labeled with tyramide (column 11, lines 1-30), which has a fluorescent label thereon (column 13, lines 30-40). Thus, modification of the method of Lea et al with the teachings of Kaplan and Hansen et al results in a method comprising a reagent material that is a fluorescently labeled nucleotide probe.

Regarding claim 115, the method of claim 87 is discussed above. Lea et al also teach the addition of lysing agents (column 4, lines 55-65). Kaplan teaches the addition of fixing agents (column 2, lines 55-67), and that the cells are tissue cells (column 3, lines 10-30).

While the cited prior art does not teach the lysing agents are added with the targeting species/labeling agent as part of the reagent material, the courts have held that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results (*In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946). See MPEP 2144.04 IV.C. Thus, modification of the method of Lea et al with the teachings of Kaplan and Hansen et al results in a method comprising lysing reagents and tissue fixing agents.

Regarding claims 116 and 138, the method of claim 87 is discussed above. Kaplan teaches the labeling agent is the fluorescence amplification agent fluorescyl-tyramine; namely, tyramine is conjugated to form tyramide (column 11, lines 1-32), and the tyramide is conjugated to fluorescein (column 13, lines 20-50).

Regarding claims 117-118, the method of claim 87 is discussed above. Lea et al also teach the labeling agent is acridine orange; namely, the beads are also attached via direct coupling to a fluorescent labeling agent, which is a dye, via a sandwich complex (column 4, line 25-column 5, line 5), wherein the fluorescent dye is acridine orange (i.e., claims 117-118).column 5, lines 34-36). In addition, Kaplan teaches the dye is the cyanine dye Cy3.29 (i.e., claims 117-118; column 1, lines 45-55).

Regarding claims 120-121, the method of claim 87 is discussed above. Lea et al further teach the image is recorded using an array of detection devices; namely, the recording is made with a CCD array (column 5, lines 9-40).

Regarding claims 122-123 and 140, the method of claim 87 is discussed above.

It is noted that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories,* 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also *Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005)(reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component); Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed."). Thus, the teaching of Lea et al that the flat image **may** be magnified encompasses the alternate embodiment wherein the image is **not** magnified (i.e., claim 122). See MPEP § 2123 [R-5]. A non-magnified image would have an enlargement ratio of 1 (i.e., claim 123). Because none of the linear dimensions are enlarged, the ratio of all of the linear dimensions of the image relative to the exposing domains equal 1, which is less than 4 (i.e., claim 140).

Regarding claim 124, the method of claim 87 is discussed above.

Hansen et al teach the method comprises gathering sufficient information in one exposure (paragraph 0026). Thus, modification of the method of Lea et al with the teachings of Kaplan and Hansen et al results in a method wherein the image is recorded in one exposure.

Regarding claim 125, the method of claim 87 is discussed above.

Hansen et al teach the method comprises gathering sufficient information in more than one exposure (paragraph 0026). Thus, modification of the method of Lea et al with the teachings of Kaplan and Hansen et al results in a method wherein the image is recorded in more than one exposure (i.e., claim 125).

Regarding claim 126, the method of claim 125 is discussed above. Lea et al also teach the assessment of the number of particles is obtained on the basis of more than four images; namely, the images are sampled as ten freeze frame pictures, which are used to assess the number of particles by identifying the number of illuminated objects (i.e., particles; column 5, lines 54-67).

Regarding claim 127, the method of claim 125 is discussed above. Lea et al further teach information about the changes in the image in course of time is used in the assessment of the number of particles; namely, the freeze frame images provide real time information about the number of illuminated objects (i.e., particles; column 5, lines 54-67).

Regarding claim 128, the method of claim 87 is discussed above.

Lea et al do not explicitly teach a distinction between at least two spectral properties of a labeling agent is used to obtain at least one quality or quantity parameter of the particles as an embodiment of the invention of Lea et al.

However, Lea et al do teach a method wherein a distinction between at least two spectral properties of a labeling agent is used to obtain at least one quality or quantity parameter of the particles; namely, the spectral properties of light scattering and

fluorescence of the particles are measured, which has the added advantage of providing information on the surface structure of the particles (i.e., cells) as well as provide information about the fluorescent labels themselves (column 1, lines 30-41).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on cells (i.e., microparticles) as taught by Lea et al in view of Kaplan and Hansen et al so that the method uses at least two spectral properties of a labeling agent to obtain at least one quality or quantity parameter of the particles as taught by Lea et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of providing information on the surface structure of the particles as well as provide information about the fluorescent labels themselves as explicitly taught by Lea et al (column 1, lines 30-41).

Regarding claim 129, the method of claim 87 is discussed above. Lea et al teach the recording of the image comprises exposing a first surface of the sample directly with excitation light from a first light means having a first light source; namely, Lea et al teach Figure 1, which shows excitation light from ultraviolet light source 2, which is a light means having a light source, entering cell 1 through a side wall and thereby directly striking a first surface of the sample, which is the collection of particles within cell 1. Lea et al further teach the particles then fluoresce (Abstract), and the fluorescence signal travels from the cell through lens 3, which is a focusing means (column 5, lines 5-

55). Light from lens 3 then passes to CCD array 5, which is a first detection means comprising at least a first detector (column 5, lines 5-55 and Figure 1).

Regarding claim 139, the method of claim 118 is discussed above.

The courts have stated:

> similar properties may normally be presumed when compounds are very close in structure. Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also In re Grabiak, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985) ("When chemical compounds have very close' structural similarities and similar utilities, without more a prima facie case may be made."). Thus, evidence of similar properties or evidence of any useful properties disclosed in the prior art that would be expected to be shared by the claimed invention weighs in favor of a conclusion that the claimed invention would have been obvious. Dillon, 919 F.2d at 697-98, 16 USPQ2d at 1905; In re Wilder, 563 F.2d 457, 461, 195 USPQ 426, 430 (CCPA 1977); In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972) (see MPEP 2144.08(d)).

The courts have also stated:

> [c]ompounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). See also In re May, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (stereoisomers prima facie obvious) (see MPEP 2144.09).

Therefore, the substitution of a Cy3, Cy5, or Cy5.5 dye for the Cy 3.29 dye of Kaplan would be considered an obvious variation over the prior art.

10. Claims 93, 103, 110-111, and 114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,451, issued 27 June 1995) in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) in view of Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claims 87-88 and 92 above, and further in view of Singer et al (U.S. Patent No. 5,728,527, issued 17 March 1998).

It is noted that while claims 110-111 and 114 have been rejected under 35 U.S.C 103(a) as described above in Section 9, the claims are also obvious using the interpretation outlined below.

Regarding claims 93, 103, 110-111, and 114, the method of claims 87-88 and 92 is discussed above in Section 9.

Hansen et al teach binding a fluorochrome to DNA (i.e., the analyte) within a somatic cell (i.e., claim 92; paragraph 0143). DNA in a somatic cell is inside the nucleus, which is an organelle (i.e., claim 93). Kaplan also teaches the analyte is a nucleic acid (column 4, lines 35-55), that the analyte is present at less than 20,000 molecules/cell (or particle; column 2, lines 15-25), and that the analyte is in a cell (column 4, lines 35-60).

However, neither Lea et al, Kaplan, nor Hansen et al specifically teach the analyte is a chromosomal DNA sequence (i.e., claim 103). Chromosomal DNA sequences within a cell are inside the nucleus, which is an organelle (i.e., claim 93). Probes that bind chromosomal DNA sequences within a cell are in situ hybridization probes (i.e., claim 111), and are a targeting species that is a nucleotide probe complementary to a sequence of an analyte species (i.e., claim 110).

However, Singer et al teach in situ hybridization probes (i.e., claim 111), which bind to specific sequences on chromosomal DNA (i.e., claim 103; column 2, lines 19-45) and are nucleotide probes complementary to a sequence of an analyte species (i.e., claim 110). Chromosomal DNA sequences are inside the nucleus, which is an organelle (i.e., claim 93) inside a cell. The oligonucleotide probes are fluorescently

labeled (column 1, lines 50-67). Singer et al further teach in situ hybridization probes have the added advantage of determining the expression level of genes during specific developmental stages (i.e., larval and embryonic stages; column 2, lines 19-45). Thus, Singer et al teach the known technique of detection chromosomal DNA within an organelle that is within a cell using in situ hybridization probes.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes in cells as taught by Lea et al in view of Kaplan and Hansen et al so that the detection is of chromosomal DNA sequences using in situ hybridization probes as taught by Singer et al to arrive at the instantly claimed invention with a reasonable expectation of success. The modification would result in a method using in situ hybridization probes (i.e., claim 111), which are a targeting species that is a nucleotide probe complementary to a sequence of an analyte species (i.e., claim 110) and is fluorescently labeled (i.e., claim 114), to bind to specific sequences on chromosomal DNA (i.e., claim 103), which are inside an organelle in the form of the nucleus within the cell (i.e., claim 93). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing determination of the expression level of genes during specific developmental stages as explicitly taught by Singer et al (column 2, lines 19-45). In addition, it would have been obvious to the ordinary artisan that the known technique of using the in situ hybridization probes as taught by Singer et al could have been applied to the method of Lea et al in view of Kaplan and Hansen et al with

predictable results because the known technique of using the in situ hybridization probes as taught by Singer et al predictably results in reliable detection of sequences within cellular analytes.

11. Claim 94 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,451, issued 27 June 1995) in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) in view of Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claims 87-88 and 92 above, and further in view of Connors et al (U.S. Patent No. 5,726,009, issued 10 March 1998).

Regarding claim 94, the method of claims 87-88 and 92 is discussed above in Section 9.

Neither Lea et al, Kaplan, nor Hansen et al teach the analyte is on the surface of an organelle (i.e., claim 94).

However, Connors et al teach the detection of an analyte on the surface of an organelle; namely, a targeting species/labeling agent in the form of a dye binds to the nuclear membrane. The nuclear membrane is the surface of the nucleus, which is an organelle and is comprised in a cell (column 6, lines 9-30). Thus, the analyte is the nuclear membrane, which is located on the surface of the organelle (i.e., claim 94). Connors et al also teach the detection of the nuclear membrane (i.e., as an analyte) has the added advantage of identifying dead cells, thereby allowing determination of the

number of viable cells in a population (column 6, lines 9-30). Thus, Connors et al teaches the known technique of detecting an analyte on the surface of an organelle.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes within cells as taught by Lea et al in view of Kaplan and Hansen et al so that the analyte detected in and analyte on the surface of an organelle as taught by Connors et al with a reasonable expectation of success. The modification would result in a method that detects the nuclear membrane, which is on the surface of an organelle (i.e., claim 94). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing determination of the number of viable cells in a population by identifying dead cells as explicitly taught by Connors et al (column 6, lines 9-30). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting an analyte on the surface of an organelle in a cell as taught by Connors et al could have been applied to the method of Lea et al in view of Kaplan and Hansen et al with predictable results because the known technique of detecting an analyte on the surface of an organelle in a cell as taught by Connors et al predictably results in reliable detection of analytes within cells.

12. Claims 102, 104, 107, and 131-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,451, issued 27 June 1995) in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) in view of Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claim 87 above, and further in view of Riabowol (U.S. Patent No. 5,877,161, issued 2 March 1999).

It is noted that while claims 102 and 107 have been broadly rejected as described in Section 9 above, claims are also obvious using the alternative interpretation outlined below.

Regarding claims 102, 104, 107, and 131-132, the method of claim 87 is discussed above in Section 9.

Neither Lea et al, Kaplan, nor Hansen et al teach detection of a cell cycle related protein (i.e., claims 102 and 104); namely, cyclin D1 (i.e., claims 131-132), which is a cell cycle protein (i.e., claims 102 and 104) that is a that is a medical marker of a disease (i.e., claim 107).

However, Riabowol teaches detection of cyclin D1, which has the added advantage of allowing detection of a state of quiescence, hyperplasticity, or neoplasia in a biological sample (column 4, lines 1-16). Thus, Riabowol teaches the know technique of detecting cyclin D1.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on or withing cells as taught by Lea et al in view of Kaplan and Hansen et al

so that the analyte detected is the cell cycle protein cyclin D1 (i.e., claims 102, 104, and 131-132), which is a marker of a disease (e.g., neoplasia; claim 107) as taught by Riabowol to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing detection of a state of quiescence, hyperplasticity, or neoplasia in a biological sample as explicitly taught by Riabowol (column 4, lines 1-16). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting the cell cycle protein cyclin D1 as taught by Riabowol could have been applied to the method of Lea et al in view of Kaplan and Hansen et al with predictable results because the known technique of detecting the cell cycle protein cyclin D1 as taught by Riabowol predictably results in reliable detection of neoplasia within cells.

13. Claims 105, 107, and 135 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,451, issued 27 June 1995) in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) in view of Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claim 87 above, and further in view of Draetta et al (U.S. Patent No 5,691,147, issued 25 November 1997).

It is noted that while claim 107 has been broadly rejected as described above in Sections 9 and 12 above, the claim is also obvious using the alternative interpretation outlined below.

Regarding claims 105, 107, and 135, the method of claim 87 is discussed above in Section 9.

Neither Lea et al, Kaplan, nor Hansen et al teach detection of the cell cycle related protein receptor (i.e., claim 105); namely, CDK4, which is a medical marker of a disease (i.e., claim 107) and is a cyclin dependent kinase (i.e., claim 135).

However, Draetta et al teach the detection of the level of CDK4 in a binding assay (column 25, line 65-column 26, line 35), wherein CDK4 is strongly implicated in the control of cell proliferation during the G1 phase (i.e., claims 105 and 135; column 1, lines 2-42). Determination of cell proliferation aids in the determination of the risk of certain disorders in humans (i.e., claim 107; column 3, lines 50-55). Thus, Draetta et al teach the known technique of detection CDK4.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on or within cells as taught by Lea et al in view of Kaplan and Hansen et al so that the detected analyte is the a cell cycle related protein receptor CDK4 (i.e., claims 105 and 135), which is a marker of a disease (i.e., claim 107) as taught by Draetta et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of aiding in the determination of the risk of certain disorders in humans by determination of the amount of cell proliferation as explicitly taught by Draetta et al (column 1, lines 2-42 and column 3, lines 50-55). In addition, it would have been

obvious to the ordinary artisan that the known technique of detecting CDK4 as taught by Draetta et al could have been applied to the method of Lea et al in view of Kaplan and Hansen et al with predictable results because the known technique of detecting CDK4 as taught by Draetta et al predictably results in reliable detection of certain disorders within human cells.

14. Claims 106, 107, and 136 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,451, issued 27 June 1995) in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) in view of Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claim 87 above, and further in view of Bitler et al (U.S. Patent No. 6,379,882 B1, issued 30 April 2002).

It is noted that while claim 107 has been broadly rejected as described above in Sections 9 and 12-13 above, the claim is also obvious using the alternative interpretation outlined below.

Regarding claims 106, 107, and 136, the method of claim 87 is discussed above in Section 9.

Neither Lea et al, Kaplan, nor Hansen et al teach detection of a marker of apoptosis (i.e., claim 106); namely, Annexin V (i.e., claim 136), which is a medical marker of a disease (i.e., claim 107).

However, Bitler et al teach detection of phosphatidylserines targeted with Annexin V, which has the added advantage of allowing quantitation of apoptotic cells

(column 12, lines 31-54). Thus, Bitler et al teach the known technique of detection of phosphatidylserines targeted with Annexin V.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on or within cells as taught by Lea et al in view of Kaplan and Hansen et al so that the analyte detected is phosphatidylserines targeted with Annexin V as taught by Bitler et al to arrive at the instantly claimed invention with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing quantitation of apoptotic cells as explicitly taught by Bitler et al (column 12, lines 31-54). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting phosphatidylserines targeted with Annexin V as taught by Bitler et al could have been applied to the method of Lea et al in view of Kaplan and Hansen et al with predictable results because the known technique of detecting phosphatidylserines targeted with Annexin V as taught by Bitler et al predictably results in reliable detection of apoptotic cells.

15. Claim 119 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,451, issued 27 June 1995) in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) in view of Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claim 87 above, and further in view of Mathies et al (U.S. Patent No. 6,100,535, issued 8 August 2000).

Regarding claim 119, the method of claim 87 is discussed above in Section 9.

While Lea et al teach scanning (column 1, lines 25-40), and while Hansen et al focusing using an optical system as well as scanning (paragraphs 0035-0037), neither Lea et al, Kaplan, nor Hansen et al teach the recording of the image comprises the use of a confocal scanner.

However, Mathies et al teach the use of confocal scanners, which have the added advantage of permitting high sample rates with simultaneous detection of multiple colors of fluorescent signals (column 5, lines 10-16). Thus, Mathies et al teach the known technique of using a confocal scanner.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising recording detection of analytes on or within cells as taught by Lea et al in view of Kaplan and Hansen et al by using a confocal scanner to record the image as taught by Mathies et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of permitting high sample rates with simultaneous detection of multiple colors of fluorescent signals as explicitly taught by Mathies et al (column 5, lines 10-16). In addition, it would have been obvious to the ordinary artisan that the known technique of using a confocal scanner to record the image as taught by Mathies et al could have been applied to the method of Lea et al in view of Kaplan and Hansen et al with predictable results because

the known technique of using a confocal scanner to record the image as taught by Mathies et al predictably results in reliable method of recording images.

16. Claims 102, 104-105, 107, 131, and 133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,451, issued 27 June 1995) in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) in view of Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claim 87 above, and further in view of Sherley et al (U.S. Patent No. 5,741,646, issued 21 April 1998).

It is noted that while claim 102 is rejected as described above in Sections 9 and 12, claim 104 is rejected as described above in Sections 12 and 14, claim 105 is rejected as described above in Section 13 above, claim 107 is rejected as described in Sections 9 and 12-14, and claim 131 is rejected as described above in Section 12 above, the claims are also obvious using the alternate interpretation detailed below.

Regarding claims 102, 104-105, 107, 131, and 133, the method of claim 87 is discussed above in Section 7.

Neither Lea et al, Kaplan, nor Hansen et al teach detection of p53 (i.e., claim 133), which is a tumor suppressor protein (i.e., claim 131), a cell cycle related protein (i.e., claims 102 and 104), a cell cycle related protein receptor (i.e., claim 105), and an indicator of disease (i.e., claim 107).

However, Sherley et al teach the detection of p53 (column 8, lines 40-60), wherein detection of p53 has the added advantage of aiding in the diagnosis of disease

that are due to changes in cell proliferative capacity (column 2, lines 40-55). Thus, Sherley et al teach the known technique of detecting p53.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising recording detection of analytes on or within cells as taught by Lea et al in view of Hansen et al so that the analyte detected is p53 (i.e., claim 133), which is a tumor suppressor protein (i.e., claim 131), a cell cycle related protein (i.e., claims 102 and 104), a cell cycle related protein receptor (i.e., claim 105), and an indicator of disease (i.e., claim 107), as taught by Sherley et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of aiding in the diagnosis of disease that are due to changes in cell proliferative capacity as explicitly taught by Sherley et al (column 2, lines 40-55). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting p53 as taught by Sherley et al could have been applied to the method of Lea et al in view of Kaplan and Hansen et al with predictable results because the known technique of detecting p53 as taught by Sherley et al predictably results in detection of a molecule known to be involved in diseases caused by alteration of cellular proliferation.

17. Claims 102, 104-105, 107, and 134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,451, issued 27 June 1995) in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) in view of Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claim 87 above, and further in view of Harvey et al (U.S. Patent No. 5,344,760, issued 6 September 1994).

It is noted that while claim 102 is rejected as described above in Sections 9, 12, and 16, claim 104 is rejected as described above in Sections 12, 14, and 16, claim 105 is rejected as described above in Sections 13 and 16 above, and claim 107 is rejected as described in Sections 9, 12-14, and 16, the claims are also obvious using the alternate interpretation detailed below.

Regarding claims 102, 104-105, 107, and 134, the method of claim 87 is discussed above in Section 9.

Neither Lea et al, Kaplan, nor Hansen et al teach detection of epidermal growth factor receptor (i.e., claim 134), which is a cell cycle related protein (i.e., claims 102 and 104), a cell cycle related protein receptor (i.e., claim 105), and an indicator of disease (i.e., claim 107).

However, Harvey et al teach the detection of EGFR (Abstract and column 3, lines 25-40), which has the added advantage of aiding in the investigation of tumors (column 3, lines 25-50). Thus, Harvey et al teach the known technique of detecting EGFR.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising recording

detection of analytes on or within cells as taught by Lea et al in view of Kaplan and Hansen et al so that the analyte detected is EGFR (i.e., claim 134), which is a cell cycle related protein (i.e., claims 102 and 104), a cell cycle related protein receptor (i.e., claim 105), and an indicator of disease (i.e., claim 107), as taught by Harvey et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of aiding in the investigation of tumors as explicitly taught by Harvey et al (column 3, lines 25-50). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting EGFR as taught by Harvey et al could have been applied to the method of Lea et al in view of Kaplan and Hansen et al with predictable results because the known technique of detecting EGFR as taught by Harvey et al predictably results in detection of a molecule known to be present in tumors.

Response to Arguments

18. Applicant's arguments filed 15 January 2009 (hereafter the "Remarks") have been fully considered but they are not persuasive for the reasons discussed below.

It is noted that the rejections above are new rejections. Applicant's arguments, as they apply to the new rejections, are considered below.

A. Applicant argues on page 17 of the Remarks that Lea et al do not teach a sheath fluid.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a sheath fluid) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

B. Applicant argues on page 18 that Lea et al uses flow cytometry.

However, Lea et al do not teach the method is performed in a flow cytometer; in fact, Leas et explicitly teach the method is an alternative to the techniques used in flow cytometry (column 4, lines 10-30).

C. In response to Applicant's arguments on page 19 of the Remarks that Lea et al "may introduce errors," MPEP 716.01(c) makes clear that "[t]he arguments of counsel cannot take the place of evidence in the record" (*In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965)). Thus, Applicant's mere arguments that Lea et al "may introduce errors" cannot take the place of evidence in the record.

In addition, it is reiterated that Lea et al do not teach the method is performed in a flow cytometer; in fact, Leas et explicitly teach the method is an alternative to the techniques used in flow cytometry (column 4, lines 10-30).

D. In response to Applicant's arguments on page 20 of the Remarks that Lea et al "does not function if the speed is reduced to zero," it is reiterated that that the arguments of counsel cannot take the place of evidence in the record. Thus, Applicant's mere arguments that Lea et al "does not function if the speed is reduced to zero" cannot take the place of evidence in the record.

E. Applicant argues on page 30 f the Remarks that Lea et al teach the cells may be lysed.

However, it is reiterated that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Thus, the teaching of Lea et al that the cells **may** be lysed encompasses the alternate embodiment wherein the cells are **not** lysed.

In addition, it is noted that Kaplan clearly teaches the binding of targeting species to analytes both within and on the cells, as discussed above.

F. In response to Applicant's arguments on page 21 of the Remarks that Lea et al provides no reasonable expectation of success in detecting a low amount of analyte detectable positions, it is reiterated that the arguments of counsel cannot take the place of evidence in the record. Thus, Applicant's mere arguments that Lea et al provides no reasonable expectation of success in detecting a low amount of analyte detectable positions" cannot take the place of evidence in the record.

In addition, it is noted that Kaplan is relied upon for the teaching of low amount of analyte detectable positions in a method where the sample is not flowing as described above.

G. In response to Applicant's arguments on page 21 of the Remarks regarding flow cytometry and zero flow rates, it is reiterated that Lea et al do not teach the method is performed in a flow cytometer; in fact, Leas et explicitly teach the method is an alternative to the techniques used in flow cytometry (column 4, lines 10-30).

H. In response to Applicant's arguments on pages 21-22 of the Remarks regarding labeling of low number analytes, it is reiterated that Kaplan is relied upon for the teaching of low amount of analyte detectable positions in a method where the sample is not flowing as described above.

I. Applicant's arguments on pages 22-24 of the Remarks regarding Griffiths et al and Baer et al have been considered but are moot in view of the new rejections above.

J. Applicant argues on pages 24-25 of the Remarks that there is no expectation of success in combining Singer et al because Singer et al is allegedly a completely different system.

It is reiterated that the arguments of counsel cannot take the place of evidence in the record. Thus, Applicant's mere arguments that there is no reasonable expectation of success cannot take the place of evidence in the record.

In addition, as noted above, Hansen et al teach binding a fluorochrome to DNA (i.e., the analyte) within a somatic cell (paragraph 0143). DNA in a somatic cell is inside the nucleus, which is an organelle. Kaplan also teaches the analyte is a nucleic acid (column 4, lines 35-55), that the analyte is present at less than 20,000 molecules/cell (or particle; column 2, lines 15-25), and that the analyte is in a cell (column 4, lines 35-60).

Thus, Singer et al is not relied upon for the teachings of the method of detection. Rather, Singer et al is merely relied upon for the teaching of in situ hybridization probes, which bind to specific sequences on chromosomal DNA (column 2, lines 19-45) and are nucleotide probes complementary to a sequence of an analyte species. Singer et al

further teach in situ hybridization probes have the added advantage of determining the expression level of genes during specific developmental stages (i.e., larval and embryonic stages; column 2, lines 19-45). Thus, Singer et al teach the known technique of detection chromosomal DNA within an organelle that is within a cell using in situ hybridization probes, and there is a reasonable expectation of success because Singer et al have bound to probes to chromosomal DNA, which is analogous to the teachings of Hansen et al regarding binding a fluorochrome to DNA (i.e., the analyte) within a somatic cell (paragraph 0143), and the teaching of Kaplan that the analyte is a nucleic acid (column 4, lines 35-55), that the analyte is present at less than 20,000 molecules/cell (or particle; column 2, lines 15-25), and that the analyte is in a cell (column 4, lines 35-60).

K. Applicant argues on pages 25-26 of the Remarks that Connors et al is completely different and thus cannot be combined in a reasonable manner to that there is a reasonable expectation of success.

It is reiterated that the arguments of counsel cannot take the place of evidence in the record. Thus, Applicant's mere arguments that there is no reasonable expectation of success cannot take the place of evidence in the record.

In addition, as noted above, Hansen et al teach binding a fluorochrome to DNA (i.e., the analyte) within a cell (paragraph 0143). DNA in a somatic cell is inside the nucleus, which is an organelle. Kaplan also teaches the analyte is a nucleic acid (column 4, lines 35-55), that the analyte is present at less than 20,000 molecules/cell (or particle; column 2, lines 15-25), and that the analyte is in a cell (column 4, lines 35-60).

Thus, Connors et al is not relied upon for the teachings of the method of detection. Rather, Connors et al is merely relied upon for the teaching of detection of an analyte on the surface of an organelle; namely, a targeting species/labeling agent in the form of a dye binds to the nuclear membrane. The nuclear membrane is the surface of the nucleus, which is an organelle and is comprised in a cell (column 6, lines 9-30). Thus, the analyte is the nuclear membrane, which is located on the surface of the organelle (i.e., claim 94). Connors et al also teach the detection of the nuclear membrane (i.e., as an analyte) has the added advantage of identifying dead cells, thereby allowing determination of the number of viable cells in a population (column 6, lines 9-30). Thus, Connors et al teach the known technique of detecting an analyte on the surface of an organelle, and there is a reasonable expectation of success because Connors et al have bound to probes to the nuclear membrane, which is analogous to the teachings of Hansen et al regarding binding a fluorochrome to DNA (i.e., an analyte within a cell; paragraph 0143), and the teaching of Kaplan that the analyte is in a cell (column 4, lines 35-60).

L. Applicant further argues on page 26 that Connors et al teach a magnification of 200:1

However, Connors et al is not relied upon for the magnification. Rather, as noted above, the teaching of Lea et al that the flat image **may** be magnified encompasses the alternate embodiment wherein the image is **not** magnified. A non-magnified image would have an enlargement ratio of 1. Because none of the linear dimensions are

enlarged, the ratio of all of the linear dimensions of the image relative to the exposing domains equal 1, which is less than 20.

M. Applicant argues on page 27 of the Remarks that Riabowol is completely different and thus cannot be combined in a reasonable manner to that there is a reasonable expectation of success.

It is reiterated that the arguments of counsel cannot take the place of evidence in the record. Thus, Applicant's mere arguments that there is no reasonable expectation of success cannot take the place of evidence in the record.

In addition, as noted above, Hansen et al teach binding a fluorochrome to DNA (i.e., the analyte) within a somatic cell (paragraph 0143). DNA in a somatic cell is inside the nucleus, which is an organelle. Kaplan also teaches that the analyte is in a cell (column 4, lines 35-60), that the analyte is a protein (column 4, lines 35-55), and that the analyte is present at less than 20,000 molecules/cell (or particle; column 2, lines 15-25).

Thus, Riabowol is not relied upon for the teachings of the method of detection. Rather, Riabowol is merely relied upon for teaching the detection of cyclin D1, which has the added advantage of allowing detection of a state of quiescence, hyperplasticity, or neoplasia in a biological sample (column 4, lines 1-16). Thus, Riabowol teaches the know technique of detecting cyclin D1, and there is a reasonable expectation of success because Riabowol has bound to probes to cyclin D1, which is analogous to the teaching of Kaplan that the analyte is in a cell (column 4, lines 35-60) and the teaching of Kaplan that the analyte is a protein (column 4, lines 35-55).

N. Applicant argues on pages 27-28 of the Remarks that Draetta is completely different and thus cannot be combined in a reasonable manner to that there is a reasonable expectation of success.

It is reiterated that the arguments of counsel cannot take the place of evidence in the record. Thus, Applicant's mere arguments that there is no reasonable expectation of success cannot take the place of evidence in the record.

In addition, as noted above, Hansen et al teach binding a fluorochrome to DNA (i.e., the analyte) within a somatic cell (paragraph 0143). DNA in a somatic cell is inside the nucleus, which is an organelle. Kaplan also teaches that the analyte is in a cell (column 4, lines 35-60), that the analyte is a protein (column 4, lines 35-55), and that the analyte is present at less than 20,000 molecules/cell (or particle; column 2, lines 15-25).

Thus, Draetta et al is not relied upon for the teachings of the method of detection. Rather, Draetta et al teach the detection of the level of CDK4 in a binding assay (column 25, line 65-column 26, line 35), wherein CDK4 is strongly implicated in the control of cell proliferation during the G1 phase (column 1, lines 2-42). Determination of cell proliferation aids in the determination of the risk of certain disorders in humans (column 3, lines 50-55). Thus, Draetta et al teach the known technique of detection CDK4, which is analogous to the teaching of Kaplan that the analyte is in a cell (column 4, lines 35-60) and the teaching of Kaplan that the analyte is a protein (column 4, lines 35-55).

O. Applicant argues on pages 28-29 of the Remarks that Bitler et al is completely different and thus cannot be combined in a reasonable manner to that there is a reasonable expectation of success.

It is reiterated that the arguments of counsel cannot take the place of evidence in the record. Thus, Applicant's mere arguments that there is no reasonable expectation of success cannot take the place of evidence in the record.

In addition, as noted above, Hansen et al teach binding a fluorochrome to DNA (i.e., the analyte) within a somatic cell (paragraph 0143). DNA in a somatic cell is inside the nucleus, which is an organelle. Kaplan also teaches that the analyte is in a cell (column 4, lines 35-60), that the analyte is a protein (column 4, lines 35-55), and that the analyte is present at less than 20,000 molecules/cell (or particle; column 2, lines 15-25).

Thus, Bitler et al is not relied upon for the teachings of the method of detection. Rather, Bitler et al teach detection of phosphatidylserines targeted with Annexin V, which has the added advantage of allowing quantitation of apoptotic cells (column 12, lines 31-54). Thus, Bitler et al teach the known technique of detection of phosphatidylserines targeted with Annexin V, which is analogous to the teaching of Kaplan that the analyte is in a cell (column 4, lines 35-60) and the teaching of Kaplan that the analyte is a protein (column 4, lines 35-55).

P. Applicant's arguments on pages 29-30 of the Remarks regarding Bobrow et al have been considered but are moot in view of the new rejections above.

Q. Applicant argues on pages 30-31 of the Remarks that Mathies et al is incompatible with Lea et al and Hansen et al

It is reiterated that the arguments of counsel cannot take the place of evidence in the record. Thus, Applicant's mere arguments that there is no reasonable expectation of success cannot take the place of evidence in the record.

In addition, as noted above, it is reiterated that Lea et al teach scanning (column 1, lines 25-40), and that Hansen et al teach focusing using an optical system as well as scanning (paragraphs 0035-0037). Mathies et al is merely relied upon for the use of confocal scanners, which have the added advantage of permitting high sample rates with simultaneous detection of multiple colors of fluorescent signals (column 5, lines 10-16). Thus, Mathies et al teach the known technique of using a confocal scanner, which is readily combined with Lea et al and Hansen et al because both Lea et al and Hansen et al teach scanning for detection.

R. Applicant argues on pages 31-32 of the Remarks that Sherley et al do not teach a detection method.

However, as noted in the rejections above, Sherley et al is merely relied upon for motivation to detect p53 (column 8, lines 40-60), wherein detection of p53 has the added advantage of aiding in the diagnosis of disease that are due to changes in cell proliferative capacity (column 2, lines 40-55). Kaplan teaches detection of an analyte in a cell (column 4, lines 35-60), that the analyte is a protein (column 4, lines 35-55), and that the analyte is present at less than 20,000 molecules/cell (or particle; column 2, lines 15-25).

S. Applicant argues on pages 32-33 of the Remarks that Harvey et al do not teach detection of particles, and thus is not combinable with Lea et al or Hansen et al.

However, as noted in the rejection above, Harvey et al is merely relied upon for motivation to detect EGFR (Abstract and column 3, lines 25-40), which has the added advantage of aiding in the investigation of tumors (column 3, lines 25-50). Kaplan teaches detection of an analyte in a cell (column 4, lines 35-60), that the analyte is a protein (column 4, lines 35-55), and that the analyte is present at less than 20,000 molecules/cell (or particle; column 2, lines 15-25).

Conclusion

19. No claim is allowed.

20'. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT T. CROW whose telephone number is (571)272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Examiner
Art Unit 1634

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